IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	EPSTEIN, et al.
Serial No.	:	09/478,621
For	:	**INHIBITING DEVELOPMENT OF MICROVESSELS WITHIN CORONARY OR PERIPHERAL VESSEL WALLS FOR RESTENOSIS/ATHEROSCLEROSIS PREVENTION OR THERAPY**
Filed		January 5, 2000
Art Unit	:	1646
Examiner	:	D. Jiang

745 Fifth Avenue
New York, NY 10151

EXPRESS MAIL

Mailing Label Number: EV 385415375 US

Date of Deposit: February 27, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" Service under 37 CFR 1.10 on the date indicated above and is addressed to: **Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Charles Jackson
(Typed or printed name of person mailing paper or fee)

Charles Jackson
(Signature of person mailing paper or fee)

DECLARATION UNDER 37 C.F.R. 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Dr. Stephen E. Epstein, declare and state that:

1. I make this declaration in connection with U.S. application Serial No. 09/478,621. I am a co-inventor of this application and am familiar with its prosecution history, particularly as it pertains to the rejection under 35 U.S.C. §103(a) of claims 1, 3-5 and 8-11 and 18-33, as allegedly being unpatentable over Inoue *et al.* and Maisonpierre *et al.* in view of Kendall *et al.* and Asahara *et al.* and in further view of Hanahan.

2. I am a U.S. citizen. As indicated on my attached *Curriculum vitiae*, I received an A.B. degree from Columbia College in 1957, and an M.D. degree from Cornell University

Medical College in 1961. I have been employed by Cardiovascular Research Institute and MedStar Research Institute since 2000, and currently hold the positions of Executive Director, and Director of Vascular Biology Research of the Cardiovascular Research Institute, MedStar Research Institute. I have practiced in the field of cardiology for over forty years, and in view of my education and experience, I am considered to be an expert in the field to which this application pertains.

3. The August 27, 2003 Office Action alleges that the combination of Inoue *et al.*, Maisonpierre *et al.*, Kendall *et al.*, Asahara *et al.* and Hanahan renders the instant invention obvious. It should be noted that, at best, the cited references relate to angiogenesis in general, and its potential role in atherosclerosis. As discussed below, atherosclerosis and restenosis are not the same condition, and, contrary to the statement on page 7 of the Office Action, it would NOT be obvious to a person of ordinary skill in the art to extend a treatment for atherosclerosis to treating restenosis.

4. Atherosclerosis and restenosis share several pathophysiologic components that lead to luminal narrowing of an artery, and thereby compromise blood flow to the tissue supplied by the artery. Among the common components are vessel remodeling (whereby the diameter of the vessel no longer expands, and may diminish, as plaque accumulates and begins to compromise lumen diameter), and smooth muscle cell proliferation and accumulation (which leads to increased plaque mass and thereby progressively to compromise of lumen diameter). Moreover, both angiogenesis and restenosis also demonstrate an increase in the number of microvessels in the vessel wall. (See Pels *et al.*, cited by the Examiner; "Pels 1").

However, the fact that these components are present in both restenosis and atherosclerosis does not mean that the mechanisms leading to restenosis and atherosclerosis are the same, nor does it mean that inhibiting the development of any of these components will have the same effect on restenosis as on atherosclerosis. The justification for this conclusion derives from multiple considerations, among the most important of which are: 1) that atherosclerosis is a ***chronic*** process, developing over many years; 2) that atherosclerosis involves not only vessel remodeling and smooth muscle cell accumulation, but also lipid accumulation, calcium deposition, development of foam cells, development of a lipid core surrounded by a fibrotic cap, development of an extensive matrix, and expression of various collagenases and elastases that might lead to plaque rupture; 3) that restenosis following arterial angioplasty is an ***acute*** process,

with the vast majority of instances of restenosis occurring within four months following acute vessel injury; and 4) that none of the other processes enumerated above (lipid accumulation, calcium deposition, development of foam cells, development of a lipid core surrounded by a fibrotic cap, development of an extensive matrix, and expression of various collagenases and elastases) is involved in the restenosis process.

Thus, although both negative vessel remodeling and smooth muscle cell accumulation are pivotal mechanisms responsible for the development of luminal narrowing in both atherosclerosis and restenosis, as indicated above, there are many other contributing mechanisms in the processes involved in atherosclerosis development that are not shared by restenosis. It is also obvious that the vessel wall responses to a chronic injury extending over many years would be very different from the vessel wall responses to an acute injury that occurs within seconds.

5. Importantly, although increased development of microvessels (angiogenesis) has been described in both atherosclerosis and restenosis, it is totally unknown what role angiogenesis plays *either* in the general processes involved in atherosclerosis or restenosis, or in the specific processes of vessel remodeling and smooth muscle cell accumulation. As Pels himself states: "The spatial correlation between arterial wall microvessels and the accumulation of atherosclerotic plaque is well documented. The role of these microvessels in the development of primary and restenotic lesions is not known." (Abstract of Arterioscler Thromb Vasc Biol. 1999 Feb;19(2):229-38; "Pels 2", copy enclosed.)

Further, Pels 1 stated: "We have considered the possibility that adventitial microvessels can have a beneficial impact on the maintenance of arterial lumen after an acute injury such as balloon angioplasty whereas intimal/medial microvessels might contribute to the growth of a plaque during a chronic atherogenic disease process" (page 899, col. 2, second sentence under "Summary and Future Directions").

6. Thus, while the Examiner is correct that 1) angiogenesis is common to both atherosclerosis and coronary restenosis, and 2) "Pels teaches that neointimal formation and arterial wall remodeling are pivotal causes of luminal narrowing in atherogenesis and restenosis" a causal relation between 1 and 2 is <u>not</u> obvious. That is, it is not obvious that angiogenesis is causally related, in *either* atherogenesis or restenosis, to neointimal formation and remodeling; and therefore, it is not obvious that angiogenesis is causally related, in *either* atherogenesis or restenosis, 1) to luminal narrowing, 2) to inhibition of luminal narrowing. In fact, the actual

experiments in Pels 2 demonstrate that regression of angiogenesis post-angioplasty is associated with luminal narrowing (see penultimate sentence in Abstract of Pels 2), which is just the opposite of what is taught in the current application.

As such, the Examiner's statement that "...it is obvious to a person of ordinary skill in the art to extend a treatment for atherosclerosis to treating restenosis" is not applicable to the instant invention, because it is not known whether inhibiting angiogenesis is beneficial for treating atherosclerosis and, if it were, whether it would also be beneficial for the treatment of restenosis. In fact, on the basis of Pels' data, a person of ordinary skill in the art would conclude that an intervention designed to inhibit angiogenesis following angioplasty would actually lead to a worsening of restenosis. Therefore, the state of the art at the time this application was filed *teaches away* from the claimed invention.

7. In view of the foregoing, it is my opinion as one of skill in the art, that, in view of the state of the art at the time of filing, it would not have been obvious to reduce restenosis by administering a combination of a VEGF inhibitor and a vessel maturation inducer. Furthermore, the combined teachings of Inoue *et al.*, Maisonpierre *et al.*, Kendall *et al.*, Asahara *et al.* and Hanahan do not lead the skilled artisan to the claimed invention, as none of these references addresses restenosis specifically. As discussed herein and in the accompanying Amendment, restenosis and atherosclerosis are distinct conditions, with distinct mechanisms, and the treatment of one cannot necessarily be extrapolated to the other. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) are requested.

8. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true. These statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2/24/04 Stephen E. Epstein

Stephen E. Epstein

CURRICULUM VITAE

STEPHEN EDWARD EPSTEIN, M.D.

Present position: Executive Director, Cardiovascular Research Institute and Director, Vascular Biology Research, MedStar Research Institute, Washington Hospital Center, Washington, D.C.

Marital status: Married, 1957. Three children

Education:

June 1957 - A.B., Summa cum laude, Columbia College
June 1961 - M.D., Cornell University Medical College

Brief Chronology of Employment:

1961-62	Intern, the New York Hospital, New York, New York.
1962-63	Resident, The New York Hospital, New York, New York
1963-66	Clinical Associate, National Heart Institute
1966-68	Senior Investigator and Attending Physician, Consulting Cardiologist to the Surgical Service, National Heart Institute
1967-68	Clinical Instructor of Medicine, Georgetown University School of Medicine, Washington, D.C.
1968-69	Acting Chief, Cardiology Branch; Chief, Section on Circulatory Physiology
1969-97	Chief, Cardiology Branch, National Heart, Lung, and Blood Institute
1971-74	Clinical Associate Professor of Medicine, Georgetown University School of Medicine, Washington, D.C.
1974-	Clinical Professor of Medicine, Georgetown University School of Medicine, Washington, D.C.
1998-	Director, Vascular Biology Research, Cardiovascular Research Institute, MedStar Research Institute, Washington Hospital Center, Washington, D.C.
1999-	Executive Director, Cardiovascular Research Institute, MedStar Research Institute, Washington Hospital Center, Washington, D.C.

Military Service:

Commissioned Corps, United States Public Health Service, July 1, 1963 to July 1, 1966; 1971 - present

Societies:

American Federation for Clinical Research
American Physiological Society
American College of Cardiology
American Heart Association
The Council on Basic Science of the American Heart Association

Member, Council on Circulation of the American Heart Association
Member, Council on Clinical Cardiology of the American Heart Association
American Society for Pharmacology and Experimental Therapeutics
Association of University Cardiologists

Honors and other special scientific recognition:
New York State Scholarship (college)
Killough Foundation Scholarship (college)
Columbia College Scholarship
New York State Medical Scholarship
The William C. Thro Prize for Clinical Pathology
The William Mecklenburg Polk Prize for Research
Phi Beta Kappa
Alpha Omega Alpha elected junior year
American Society for Clinical Investigation
Member of Board of Governors (Public Health Service), American College of Cardiology, 1977-1980.
Association of American Physicians
Judge, Young Investigators Award, American College of Cardiology, 1977
Plenary Address - American College of Cardiology Annual Meeting: Atlanta, 1986.
Honorary Fellow, American College of Chest Physicians, 1987.
Distinguished Service Medal, Public Health Service, 1990
Keynote Lecture- 8th SE Lipid Conference: Atlanta, 1999
Plenary Address – American Heart Association Annual Meeting: 1999
Distinguished WELCOME Lecturer, St. Boniface General Hospital Research Center: Winnipeg, 1999
Plenary Address- XXI Congress-European Society of Cardiology: Barcelona, 1999
State of the Art Lecture: Angiogenesis- AHA Annual Meeting, 2000
Pfizer Visiting Professor Program, Cardiology Division, L.D.S. Hospital, Salt Lake City, 2001
Invited Lecture, ACC Annual Meeting 2002: Viruses and Vascular Disease.
Fellow of the American Heart Asociation, Council on Clinical Cardiology (F.A.H.A.) 2001
Fellow of the American Heart Association, Council on Basic Cardiovascular Sciences (F.A.H.A.) 2001
Invited Lecture, ACC Annual Meeting 2002: Myocardial Angiogenesis—Gene Therapy.
Invited Lecture, ACC Annual Meeting 2002: Infectious Pathogens in Coronary Artery Disease: Important for Risk or Innocent Bystander?
DSMB-member: Programs of Excellence in Gene Therapy for the Heart, Lung, and Blood Institute, 2000-present.
Invited Lecture, AHA Annual Meeting 2003: Overview of Angiogenesis
Invited Lecture, ACC Annual Meeting 2004: Stem Cell Therapy: State of the Art

Editorial Board Appointments:
Circulation 1974-
Journal of Clinical Investigation 1977-1982

American Journal of Cardiology 1978-1996
Cardiovascular Medicine 1979-1985
Journal of the American College of Cardiology, 1986-1994

Committee Appointments:
NHLBI Gene Therapy Data Safety and Monitoring Board, 2001-
Medical Advisory Board, Council on Circulation-end, 1992
Executive Committee, Council on Circulation, end, 1994
National Heart, Lung, and Blood Institute Fellowship Board, end, 1995
Clinical Research Committee, National Institutes of Health, end 1990
Clinical Research Committee, National Heart Lung and Blood Institute, end 1998
Chief, Medical Care Consultant Panel in Cardiovascular Diseases, NIH, end 1985
Program Committee - Council on Circulation; Annual AHA Meeting, 1979
Credentials Committee, Council on Circulation, AHA, 1980
Search Committee for Director; Division of Heart and Vascular Diseases, NIH - 1977.
Search Committee for Director, Division of Heart and Vascular Diseases, NIH - 1979
Search Committee for Director, National Heart, Lung, and Blood Institute, NIH - 1982
Search Committee for Chief of Nuclear Medicine, Clinical Center, NIH, 1982.
Search Committee for Chief of Cardiac Surgery, NHLBI, 1983
Continuing Education Committee for Extramural Programs, Amer. College of Cardiology, 1984-1996
Medical Advisory Council of Variety Children's Lifeline
WHO Expert Advisory Panel on Cardiovascular Disease, 1982-
Annual Scientific Session Program Committee, American College of Cardiology - 1987
Committee on Exercise and Cardiac Rehabilitation, Council on Clinical Cardiology, American Heart Association.
Member, Advisory Committee of the Cardiac Research Center, Ben-Gurion University of the Negev,
Beer Sheva, Israel
Leadership Council, MedStar Research Institute, Washington Hospital Center, Washington, DC.

Named Lectureships:
Higginbotham Orator, Baylor University Medical Center, 1977.
Canadian Heart Foundation Guest Lectureship, 1978.
Harold H. Bix Lecturer, 1978, Baltimore, Maryland.
James B. Herrick Memorial Lecture, Chicago Heart Association, 1979.
George R. Herman Lectureship, University of Texas Medical Branch at Galveston, 1980.
John N. Edson Lectureship in Medicine, Long Island College of Medicine, 1982.
Bernard D. Rosenblum Memorial Lecture, American Heart Association, Louisville, Kentucky, 1982.
Ramon L. Lange Memorial Lecture, Medical College of Wisconsin, 1983.
Hammond Lecturer, St. John's Mercy Medical Center, St. Louis, Missouri, 1983.
Kenneth Rosen Memorial Lecture; University of Illinois at Chicago, 1984.
William L. MacDonald Lecturer; Heart & Stroke Foundation of Ontario, 1985.
Amon G. Carter Visiting Professor, University of Texas Health Science Center at Dallas,

1986.
Hugo Roesler Memorial Lecture, Temple University, Philadelphia, Pa. 1986.
Plenary Address. American College of Cardiology Annual Meeting, Atlanta, Georgia, 1986.
Honorary Fellow Lecturer, Amer. College of Chest Physicians Annual Meeting; Atlanta, Georgia, 1987.
Paul Block Memorial Lecture, Monmouth Medical Center, Long Branch, New Jersey, 1988.
Yoshio Mikamo Memorial Lecture, 54th Annual Scientific Mtg. of the Japanese Circul. Society, 3/1990.
David Littmann Lecture, Harvard Medical School, Boston, Mass., May 3, 1990.
Gordon H. Ira Jr., M.D., Medical Lectureship, St. Luke's Hosp., Ponte Vedra, Florida, January 20, 1993.
Miriam Lemberg Visiting Professorship in Cardiovascular Disease, University of Miami School of Medicine, Miami, Florida, March 3, 1993.
Neufeld Memorial Lecture, Israel Heart Society, Tel Aviv, Israel, April 20, 1993.
Emanuel Klosk Lectureship in Cardiology, Newark Beth Israel Hospital, December 14, 1995.
Henry J. Russek Lecture, Twenty-Ninth Annual New York Cardiovascular Symposium of the American College of Cardiology, New York, NY, December 13-15, 1996.
Herbert Berger Lecture, University of Maryland School of Medicine, March 27, 1997.
The Don C. and George C. Sutton Memorial Lectureship in Cardiology, Evanston Hospital, September 1998.
Dr. ER Smith Lectureship in Cardiovascular Health, University of Calgary, November 1998
Invited Lecture, ACC Annual Meeting 2001: Myocardial Angiogenesis—Gene Therapy.
Invited Lecture, ACC Annual Meeting 2001: Infectious Pathogens in Coronary Artery Disease: Important for Risk or Innocent Bystander?
Invited Lecture, ACC Annual Meeting 2001: Viruses and Vascular Disease.
Pfizer Visiting Professorship Program in Cardiology, University of Utah School of Medicine, September, 2001.

Patents:

Tech ID No. 08/136,113, entitled, "Efficient and Selective Adenoviral-Mediated Transfer into Vascular Neointima." Inventors: R. Crystal, S. Epstein, T. Finkel and R. Guzman.

Patent No. 5,756,476 (issued May 26, 1998), entitled, " Inhibition of Cell Proliferation Using Antisense Oligonucleotides." Inventors: S. Epstein, E. Unger and E. Speir.

Patent No. 5,244,460 (issued), entitled, "Method To Foster Myocardial Blood Vessel Growth And Improve Blood Flow To The Heart." Inventors: E. Unger and S. Epstein.

Patent No. 6,183,752 (issued), entitled, "Restenosis/atherosclerosis diagnosis, prophylaxis and therapy." Inventors: S. Epstein et al.

CRADAs

GenVec, "Adenoviral Gene Transfer for the Treatment of Cardiovascular Diseases." Total funds provided to NHLBI by company: $37,500

Pasteur Merieux, "Development of a Safe and Effective Treatment for Restenosis and Atherosclerosis." Total funds provided to NHLBI by company: $88,257

Short Biographical Sketch
Stephen E. Epstein, M.D.

After graduating Summa Cum Laude from Columbia College I completed my medical training at Cornell University Medical College and interned at the New York hospital, New York, NY. I then joined Dr. Eugene Braunwald at the National Heart Institute, NIH, as a Clinical Associate. When Dr. Braunwald left the NIH, I was asked to assume his position, and became Chief of the Cardiology Branch, NHLBI in 1969. In that capacity I was in charge of all clinical and research programs, and over the course of my almost thirty year tenure there, published over four hundred papers in peer-reviewed journals. My areas of interest over those years were hypertrophic cardiomyopathy, valvular heart disease, and the determinents of myocardial injury during acute myocardial infarction. Over the past decade my major research interests have focused on the role of infection in atherosclerosis, and the development of therapeutic strategies to enhance collateral development in patients with coronary artery and peripheral vascular disease. The research efforts include basic molecular and cell biology investigations to elucidate mechanisms, and clinical investigations to translate the basic investigations to the clinical arena.

In 1998 I was recruited to develop and head a molecular and cell biology program at the Cardiovascular Research Foundation (CRF) at the Washington Hospital Center. Shortly thereafter the Cardiovascular Research Institute (CRI), a division of the MedStar Research Institute, was formed taking the place of CRF. I was asked to assume the additional responsibility of being the Executive Director of CRI, which I did and in which capacity I am functioning through the present time.

Here at the Washington Hospital Center I am responsible for all of the cardiovascular research of the MedStar Research Institute, which is the research arm of MedStar Health (an umbrella organization that owns and operates five hospitals in the Washington/ Baltimore area including the Washington Hospital Center and Georgetown University Hospital). CRI is one of the largest divisions of MRI; it is composed of senior cardiovascular investigators, interventional cardiologists, research nurses, technicians, and support staff who are dedicated to developing new technologies and strategies to enhance the cardiovascular care of patients. The goals of CRI are implemented by a commitment to a strong basic research program to further the understanding of the causative mechanisms responsible for cardiovascular disease, and an equally strong commitment to translating the fruits of this research to the treatment and diagnosis of patients.